

# Frusemide and Its Acyl Glucuronide Show a Short and Long Phase in Elimination Kinetics and Pharmacodynamic Effect in Man

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## Abstract

The pharmacokinetics of 80 mg frusemide given orally were investigated in normal subjects using a direct HPLC method for parent drug and its acyl glucuronide conjugate.

Two half-lives could be distinguished in the plasma elimination of both frusemide and its conjugate, with values of  $1.25 \pm 0.75$  and  $30.4 \pm 11.5$  h for frusemide and  $1.31 \pm 0.60$  and  $33.2 \pm 28.0$  h for the conjugate. The renal excretion rate-time profile showed two phases; the rapid elimination phase lasted from 0-15 h and the second and slow phase, from 15-96 h. During the first 15 h,  $33.3 \pm 4.8\%$  of the dosed frusemide was excreted; in the remaining period 15-96 h,  $4.6 \pm 1.5\%$  was excreted. In the same two periods the excretion of the glucuronide was  $13.4 \pm 4.7$  and  $1.9 \pm 1.1\%$ , respectively. The mean renal clearance of frusemide was  $90.2 \pm 16.9$  mL min<sup>-1</sup> during the first period and  $91.5 \pm 29.3$  mL min<sup>-1</sup> in the remaining period, during which the stimulation of urine production was absent. The renal clearance of the acyl glucuronide was  $702 \pm 221$  mL min<sup>-1</sup> in the first period, but only  $109 \pm 51.0$  mL min<sup>-1</sup> in the second period. The stimulated urine production in the first 6 h after administration amounted to  $2260 \pm 755$  mL (measured urine production minus baseline value of 1 mL min<sup>-1</sup> (360 mL). During the second or rebound period (6-96 h after drug administration), the quantity of urine was  $990 \pm 294$  mL lower than what would have been expected from the baseline production of 5400 mL. This reduced production (0.82 mL min<sup>-1</sup>) is equivalent to an 18% reduction in the average urine flow rate of 1 mL min<sup>-1</sup>.

Frusemide (4-chloro-*N*-(2-furylmethyl)-5-sulphamoylanthranilic acid, pK<sub>a</sub> 3.9) inhibits the active reabsorption of chloride ions in the thick ascending limb of the loop of Henle by binding to one of the Cl<sup>-</sup> binding sites of the Na<sup>+</sup>/2Cl<sup>-</sup>/K<sup>+</sup> co-transport system. In man, frusemide is metabolized to its acyl glucuronide (Beerman et al 1975, 1977). Acyl glucuronides are unstable in alkaline media (pH > 7.0); therefore, for analysis urine must be kept acidic at pH 5.0 in order to prevent hydrolysis and isomerization of acyl glucuronides even before excretion (Faed 1984; Rachmel et al 1985; Vree et al 1992a, 1993a, b).

The reported half-lives (t<sub>1/2</sub>) of frusemide and its glucuronide are of the order of 2 h (Hammarlund et al 1985; Vree et al 1994, 1995b). In a pilot experiment in our laboratory, a second, long half-life of frusemide and its acyl glucuronide became visible (Vree et al 1994).

Hammarlund et al (1985) mentioned the effect of an acute tolerance to frusemide's effect as being a homeostatic adaptive response to the acute loss of salt or water. This homeostatic response, which Reyes called a rebound effect (Reyes 1991), may also be the result of a prolonged disposition of frusemide at the Cl<sup>-</sup> binding sites.

The aim of this investigation was to study the pharmacokinetics of frusemide and its acyl glucuronide in healthy volunteers, to assess the long half-life of parent drug and glucuronide conjugate, and to analyse the diuretic and antidiuretic response.

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## Materials and Methods

### Drugs and chemicals

Frusemide and Lasix (40 mg tablets) were obtained from Hoechst (Amsterdam, Netherlands and Frankfurt, Germany). All other reagents were of analytical grade and obtained from Merck (Darmstadt, Germany).

Frusemide acyl glucuronide was isolated and identified in human urine after administration of 80 mg frusemide (Vree et al 1994).

### Subjects

Seven human subjects (4 males (non-smokers), 3 females (one smoker), mean age  $34 \pm 7$  years, mean bodyweight  $80 \pm 6$  kg) participated in the study. The volunteers took 80 mg frusemide orally (as Lasix) after an overnight fast. The study had the approval of the hospital ethics committee, and informed consent was obtained from the volunteers.

### Sampling

Fingertip blood samples (2 mL), obtained with Monolet lancets (Monoject, St Louis, USA), were collected in heparinized Eppendorf vials (2 mL) at regular time intervals during 72 h following drug administration. After centrifugation, plasma samples were stored at  $-20^{\circ}\text{C}$  pending analysis.

Urine was collected upon untimed voiding. The total time of sample collection was 96 h. Urinary pH was kept acidic (pH 5.0-5.5) by the oral intake of 1 g ammonium chloride four times per day (Ammonchlor, Südmedica, Munich, Germany). Four urine samples of 5 mL from each void

were immediately stored at  $-20^{\circ}\text{C}$  pending analysis. Total sampling time of urine was 96 h.

Each urine void (200–400 mL) was followed by ingestion of 100 mL water during the first period of 6 h.

#### Drug analysis

Frusemide and its acyl glucuronide were assayed by HPLC as reported elsewhere (Vree et al 1994). The limit of quantitation of frusemide in plasma was  $7\text{ ng mL}^{-1}$ , and for the glucuronide  $10\text{ ng mL}^{-1}$ . The limits of quantitation in urine were 100 and  $150\text{ ng mL}^{-1}$  for the parent drug and glucuronide, respectively.

The intra- and interday variation of frusemide and glucuronide in plasma and urine was  $<5\%$ . Recovery of frusemide after deproteinization of plasma was  $91.5 \pm 5.1\%$ , and that of the glucuronide was  $85.5 \pm 4.7\%$ .

Plasma samples ( $100\text{ }\mu\text{L}$ ) were deproteinized with  $100\text{ }\mu\text{L}$  acetonitrile and centrifuged at  $3000g$ ;  $20\text{ }\mu\text{L}$  of the supernatant was injected onto the column. The plasma samples were immediately injected onto the column. A stability test has shown that the glucuronide was stable at pH 7.4 for only 30 min.

Urine samples were diluted with an equal volume of water, and  $20\text{ }\mu\text{L}$  of that mixture was injected onto the column. The sample tray of the autosampler was protected from light.

#### Plasma binding

The in-vivo protein binding of frusemide and glucuronide was measured in volunteer plasma samples by means of the

Amicon Micropartition system MPS-1 (Grace BV, Amico Division, Capelle aan de IJssel, The Netherlands). The average protein binding ( $\pm$ s.d.) was calculated from two plasma samples from each volunteer obtained at maximal plasma concentration, 1–2 h after administration. No specific drug binding to the filters was observed.

#### Data analysis

Curve fitting was carried out ( $r^2 > 0.97$ ), and the pharmacokinetic parameters of the plasma concentration-time curves, renal excretion rate-time profiles, and urine flow-time profiles were calculated using the MediWare computer program (Proost & Meyer 1992). Areas under the concentration-time curves (AUC) were determined by the linear trapezoidal rule. Oral clearance ( $\text{CL}_O$ ) and mean residence time (MRT) were calculated by standard methods (Proost & Meyer 1992).

The renal clearance during the appropriate period was calculated by dividing the amount excreted in the urine during this period by the corresponding AUC value. Non-renal clearance was defined as the oral clearance minus the renal clearance.

Recovery-, or rebound-time of the urine flow was defined as the time elapsed between the end of the urine flow stimulation at which the urine flow was  $<1\text{ mL min}^{-1}$  and the time at which the urine flow reached again the value of  $>1\text{ mL min}^{-1}$ .

Analysis of variance was carried out by standard procedures, and statistical difference was defined at  $P < 0.05$ .

## Results

Fig. 1 shows the plasma concentration-time curves and renal excretion rate-time profiles of frusemide and its acyl glucuronide in one representative subject, in which the slow elimination phase is visible in both the plasma and urine curves.

Table 1 summarizes pharmacokinetic parameters of frusemide in plasma and Table 2, the parameters in urine.

Frusemide is quickly absorbed as can be concluded from the small values of  $t_{\text{lag}}$ ,  $t_{\text{max}}$ , and  $t_{1/2}$  of absorption. The lag time in blood for frusemide is  $0.29 \pm 0.16\text{ h}$  and of frusemide acyl glucuronide  $0.32 \pm 0.24\text{ h}$ , ( $P = 1.0$ ). Both compounds were also quickly excreted; the  $t_{\text{lag}}$  of the compounds in urine do not differ significantly and did not differ from those in plasma.

Two half-lives ( $\alpha$  and  $\beta$ ) can be distinguished in the plasma elimination of both frusemide and its conjugate. The  $t_{1/2\alpha}$  values of frusemide and its acyl glucuronide were  $1.25 \pm 0.75$  and  $1.31 \pm 0.60\text{ h}$ , respectively, which are not significantly different.

The plasma concentration- and renal excretion rate-time curves run parallel, resulting in similar values of the calculated pharmacokinetic parameters; plasma and urine  $t_{1/2\beta}$  values of frusemide are respectively  $33.2 \pm 28.0$  and  $29.7 \pm 21.9\text{ h}$ . The corresponding values for frusemide acyl glucuronide are  $30.4 \pm 11.5$  and  $29.9 \pm 20.2\text{ h}$ .

Although the long elimination half-life of frusemide and its acyl glucuronide in plasma was visible in five out of the seven volunteers, it was clearly visible in the urinary excretion curves of all volunteers ( $29.7 \pm 21.9\text{ h}$ ,  $\text{CV} = 73.7\%$ ).

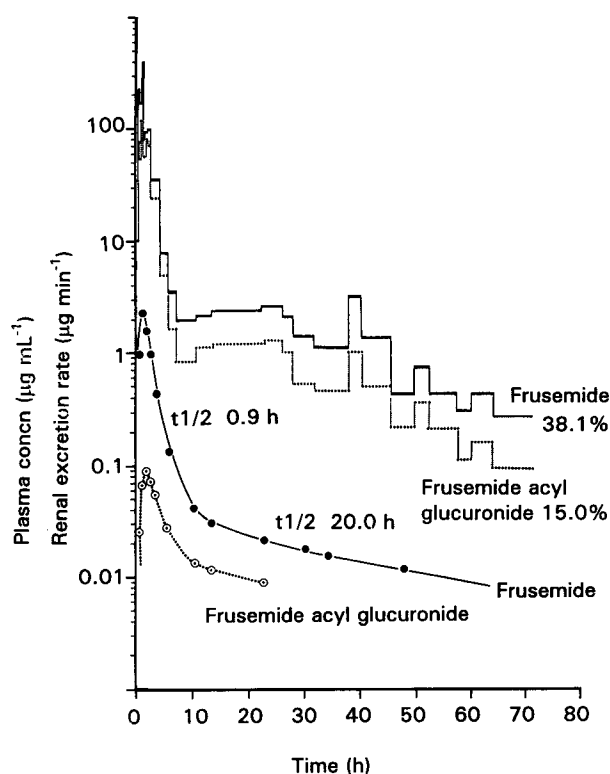


FIG. 1. Plasma concentration-time curve and renal excretion rate-time profile of frusemide and frusemide acyl glucuronide in a representative volunteer after an oral dose of 80 mg frusemide. The long  $t_{1/2\beta}$  is visible in both the plasma and the urine curve.

Table 1. Pharmacokinetic parameters in plasma of frusemide (80 mg) (n = 7).

Parameter	Frusemide	Acyl glucuronide	P
F	0.53 ± 0.07	0.15 ± 0.04	0.0003
t <sub>lag</sub> (h)	0.29 ± 0.16	0.32 ± 0.24	> 0.80
t <sub>max</sub> (h)	1.98 ± 0.98	1.50 ± 0.74	0.58
C <sub>max</sub> (μg mL <sup>-1</sup> )	2.20 ± 0.84	0.11 ± 0.07	0.0156
t <sub>2abs</sub> <sup>1</sup> (h)	0.30 ± 0.26	0.68 ± 0.50	0.034
t <sub>2α</sub> <sup>1</sup> (h)	1.25 ± 0.75	1.31 ± 0.60	0.47
t <sub>2β</sub> <sup>1</sup> (h)	33.2 ± 28.0	30.4 ± 11.5	1.00
MRT (h)	10.2 ± 11.6	14.8 ± 15.9	0.81
CL <sub>O</sub> (mL min <sup>-1</sup> )	131 ± 26.5		
CL <sub>R</sub> (mL min <sup>-1</sup> )			
0–15 h	90.2 ± 16.9	702 ± 221	
15–96 h	91.5 ± 29.3	109 ± 51.0	
CL <sub>NR</sub> (mL min <sup>-1</sup> )			
0–15 h	41.0 ± 16.5		
15–96 h	32.1 ± 19.6		
Vd <sub>ss</sub> (L)	21.9 ± 12.3	94.8 ± 68.9	0.0013
Excreted (% dose)			
0–15 h	33.3 ± 4.8	13.4 ± 4.7	< 0.0001
15–96 h	4.6 ± 1.5	1.9 ± 1.1	< 0.0001
Protein binding (%)	98.0 ± 2.0	96.1 ± 2.0	0.0284

P difference between frusemide and its acyl glucuronide.

The large coefficient of variation was caused by two volunteers showing extremely long half-lives of 37.8 h and 73.7 h (mean 55.8 ± 25.4 h; CV = 45.5%). The other five volunteers showed a much more consistent half-life of 16.4 ± 1.94 h (11.8%).

For frusemide acyl glucuronide the mean half-life in urine was 29.9 ● 20.2 h (67.6%). The great variation was caused by three volunteers showing long half-lives of 37.8, 54.4, and 58.6 h (50.3 ± 11.0 h; 21.9%). The other four volunteers showed a relatively short half-life of 14.6 ± 2.63 h (18.0%).

#### Protein binding

The protein binding of frusemide (98.0 ± 2.0%) is significantly higher than that of the acyl glucuronide (96.1 ± 2.0%, P = 0.0284).

#### Percentage of the dose excreted in the urine

The main compound in the urine was frusemide. The renal

excretion rate-time profile showed two phases, the rapid elimination phase lasting from 0–15 h, and the second, slow phase from 15–96 h.

During the first 15 h, frusemide excreted accounted for 33.3 ± 4.8% of the dose; in the remaining 15–96-h period, 4.6 ± 1.5% was excreted. In the same two periods, the percentage frusemide acyl glucuronide excreted was 13.4 ± 4.7%, and 1.9 ± 1.1%, respectively. In total, 46.7 ± 8.3% was excreted during the first 15 h, and 6.4 ± 2.1% during the remaining 15–96-h period. During the entire period (96 h), 53.0 ± 7.2% of the dose was recovered from the urine.

#### Renal clearance

The mean renal clearance of frusemide was calculated for the two elimination phases and was found to be 90.2 ± 16.9 mL min<sup>-1</sup> during the first period (0–15 h), and 91.5 ± 29.3 mL min<sup>-1</sup> during the remaining 15–96 h period,

Table 2. Pharmacokinetic parameters in urine of frusemide (80 mg) (n = 7).

Parameter	Frusemide	Acyl glucuronide	P
t <sub>lag</sub> (h)	0.20 ± 0.17	0.42 ± 0.24	0.068
t <sub>max</sub> (h)	0.86 ± 0.51	1.19 ± 0.44	0.24
U <sub>max</sub> (μg min <sup>-1</sup> )	177 ± 34.0	92.6 ± 36.5	0.0007
t <sub>2abs</sub> <sup>1</sup> (h)	0.32 ± 0.34	0.37 ± 0.42	0.80
t <sub>2α</sub> <sup>1</sup> (h)	1.23 ± 0.47	1.45 ± 0.51	0.35
t <sub>2β</sub> <sup>1</sup> (h)	29.7 ± 21.9	29.9 ± 20.2	> 0.8
MRT (h)	11.1 ± 10.4	11.7 ± 7.9	> 0.8
Excreted (%)			
0–15 h	33.3 ± 4.8	13.4 ± 4.7	< 0.0001
15–96 h	4.6 ± 1.5	1.9 ± 1.1	0.0018
Total excreted (%)			
0–15 h		46.7 ± 8.3	
15–96 h		6.4 ± 2.1	0.0001*
0–96 h		53.0 ± 7.2	0.15**

P difference between frusemide and glucuronide; \*between 0–15 h and 15–96 h; \*\*between 0–15 h and 0–96 h. \*Change between initial and final elimination in the urine profile.

Table 3. Mean urinary diuresis parameters of frusemide (80 mg) (n = 7).

Parameter	Mean $\pm$ s.d.	P
Diuresis		
$t_{lag}$ (h)	0.18 $\pm$ 0.19	
$t_{max}$ (h)	0.77 $\pm$ 0.52	
$U_{max}$ (mL min <sup>-1</sup> )	21.3 $\pm$ 6.1	
$t_{\frac{1}{2}}$ (h)	0.76 $\pm$ 0.26	
MRT (h)	2.59 $\pm$ 0.82	
$t_{effect}$ (h)	5.5 $\pm$ 0.5	
$t_{rebound}$ (h)	64.7 $\pm$ 14.4	
Urine production (mL)*		
0-6 h	+2260.0 $\pm$ 755	0.0014**
6-96 h	-990.0 $\pm$ 294	

\*Urine production exceeding the baseline value of 1 mL min<sup>-1</sup>.

\*\*P value, difference between the two periods of urine production.  $t_{effect}$ ,  $t_{rebound}$ , time course of the effect.  $U_{max}$  maximal urine production.

in which there was no stimulation of urine production. The clearance values in both periods were similar ( $P > 0.8$ ) (Table 1).

The renal clearance of the acyl glucuronide was 702  $\pm$  221 mL min<sup>-1</sup> in the first period but significantly decreased to 109  $\pm$  51.0 mL min<sup>-1</sup> in the second period ( $P = 0.0083$ ).

#### Urine production

The stimulated urine production in the first 6 h after administration amounted to 2260  $\pm$  755 mL (measured urine production minus baseline value of 1 mL min<sup>-1</sup> (360 mL) (Table 3).

During the second or rebound period of 6-96 h after drug administration the average urine production was 990  $\pm$  294 mL lower than what would have been expected from the baseline production of 5400 mL. This reduced production is equivalent to an 18% reduction in the baseline urine flow rate of 1 mL min<sup>-1</sup> (0.82 mL min<sup>-1</sup>).

The recovery- or rebound-time of the urine flow lasted 64.7  $\pm$  14.4 h (CV = 22.3%).

Table 4 compares the plasma concentration and renal excretion rates of frusemide and its glucuronide at the onset and end of stimulation of the urine production.

## Discussion

#### Pharmacokinetics

This study shows that frusemide and its acyl glucuronide

exhibit two half-lives. The short half-life of approximately 2 h is well known and related to the pharmacodynamic effect of the stimulation of the overall urine production. The second half-life of approximately 20-30 h has not been reported previously. During this slow elimination phase, only 4.6  $\pm$  1.5% of the administered dose is excreted, which is 14% of the amount excreted during the first 15 h.

During the first phase, 13.4% of the acyl conjugate is excreted, and during the second phase, only 1.9  $\pm$  1.1%, which is 14% of the first phase and the same percentage reported for frusemide.

The short  $t_{\frac{1}{2}}$  values of frusemide and its acyl glucuronide in plasma give rise to the assumption that both compounds are excreted by glomerular secretion plus active tubular secretion. Indeed, the apparent renal clearance of frusemide was 90 mL min<sup>-1</sup>, which is similar during the first and second phases of elimination.

The apparent renal clearance value of the acyl glucuronide is high during the first phase (0-6 h; 702  $\pm$  221 mL min<sup>-1</sup>) and lower in the second phase (109  $\pm$  51.0 mL min<sup>-1</sup>). In the second phase, the renal clearance values of frusemide and its acyl glucuronide are similar. The extreme high renal clearance of the acyl glucuronide during the first phase may be the result of hepatic and renal formation of the glucuronide (Smith & Benet 1983; Vree et al 1992a, b); the latter ceased in the second phase of the elimination. Probenecid inhibits the renal clearance of both frusemide (Chennavasin et al 1979; Smith et al 1980; Vree et al 1995b) and its acyl glucuronide (Vree et al 1995b).

The relation between stimulation of the urine production and the renal formation of the acyl glucuronide may be coincidental, or it may indicate that the pharmacodynamic effect is the result of the action of the renal acyl glucuronide.

#### Onset and offset of the effect

The pharmacodynamic activity of frusemide is believed to be produced as follows. The compound passes the kidney (in the thick ascending part of Henle's loop), until its concentration or excretion rate reaches 21  $\mu$ g min<sup>-1</sup> (Koajarern et al 1982); the reabsorption of the Cl<sup>-</sup> ions is inhibited, resulting in a decrease in water reabsorption and increase in overall urine flow.

Indeed, as soon as frusemide and its acyl glucuronide appear in the urine after a similar lag time, the urine flow increases.

Table 4 shows that in our group of subjects, a frusemide renal excretion rate of 28.0  $\pm$  2.9  $\mu$ g min<sup>-1</sup> (10.4 %CV) in the

Table 4. Comparison of the urine flows, plasma concentrations, and renal excretion rates of frusemide and frusemide acyl glucuronide at the onset and end of the effect (mean  $\pm$  s.d.) (n = 7).

Parameter	Start/onset	End	P
Urine flow (mL min <sup>-1</sup> )	8.04 $\pm$ 4.60	1.81 $\pm$ 0.47	0.0010
Plasma			
Frusemide ( $\mu$ g mL <sup>-1</sup> )	1.06 $\pm$ 0.45	0.44 $\pm$ 0.17	0.0014
Acyl glucuronide ( $\mu$ g mL <sup>-1</sup> )	0.059 $\pm$ 0.062	0.046 $\pm$ 0.020	0.55
Urine			
Frusemide ( $\mu$ g min <sup>-1</sup> )	62.9 $\pm$ 58.1	28.0 $\pm$ 2.9	0.0930
Acyl glucuronide ( $\mu$ g min <sup>-1</sup> )	14.9 $\pm$ 14.2	19.0 $\pm$ 10.8	0.5039

elimination phase of the kinetic curve is correlated with the end of the stimulation of the urine production. The corresponding excretion rate of the acyl glucuronide is  $19.0 \pm 10.8 \mu\text{g min}^{-1}$  ( $\text{CV} = 56.8\%$ ). During the onset of the pharmacodynamic effect, the processes occur much faster, producing a larger coefficient of variation. For the first urine sample, the average urine production is already  $8.0 \pm 4.6 \text{ mL min}^{-1}$  ( $57.5\%$ ) with a frusemide excretion rate of  $62.9 \pm 58.1 \mu\text{g min}^{-1}$  ( $92.6\%$ ) and an acyl glucuronide value of  $14.9 \pm 14.2 \mu\text{g min}^{-1}$  ( $94.8\%$ ). Strikingly, the pharmacodynamic effect starts and ends with excretion rates for the acyl glucuronide that do not differ ( $P = 0.50$ ). The large difference and coefficients of variation of the excretion rates of frusemide in the first urine sample and onset of the pharmacodynamic effect makes the difference between onset and end of effect not statistically different.

Similar data can be derived for the plasma concentration of parent compound and metabolite and the start and end of the urine flow stimulation (Table 4).

A great difference is observed between frusemide plasma concentration at onset and end of the urine flow stimulation ( $P = 0.0014$ ). This is not observed for the frusemide acyl glucuronide for which the concentrations are not significantly different ( $P = 0.55$ ).

The stimulation of the urine production faded ( $< 1 \text{ mL min}^{-1}$ ) when the renal excretion rate of frusemide drops below the threshold of  $20 \mu\text{g min}^{-1}$ , as reported by Kojarern et al (1982). During the absorption phase, this value was already achieved in the second urine sample within 1 h of oral administration. The onset looks like an instantaneous maximum effect for an 80-mg dose.

### Rebound

The pharmacodynamic effect-time curve shows a biphasic character. First, there is binding to one of the  $\text{Cl}^-$  binding sites of the  $\text{Na}^+/\text{2Cl}^-/\text{K}^+$  co-transport system of the thick ascending part of the loop of Henle, resulting in an increase of the urine production greater than  $1 \text{ mL min}^{-1}$  (Greger & Schlatter 1983; Wittner et al 1991; Swan 1994). A rebound phase follows in which the urine production is less than the baseline value of  $1 \text{ mL min}^{-1}$ .

During the pharmacodynamic effect,  $2260 \pm 755 \text{ mL}$  was excreted above the baseline value of  $1 \text{ mL min}^{-1}$  for the unmedicated and well-hydrated subjects. Despite the fact that the subjects maintained their normal drinking and eating patterns, during this excess urine excretion period, it took three days for the body to regain this amount of fluid. The average urine production over those three days was  $990 \pm 294 \text{ mL}$  less than what would have been excreted with the baseline value of  $1 \text{ mL min}^{-1}$ .

The baseline urine production of  $1 \text{ mL min}^{-1}$  ( $= 1440 \text{ mL}$  in 24) was taken as a conservative estimate; the subjects showed values of  $1\text{--}2 \text{ mL min}^{-1}$  in other long-lasting pharmacokinetic experiments with naproxen (Vree et al 1993a, b) and sulphamethoxazole (Vree et al 1995a).

This time course of the rebound effect was subjectively felt to be three days, as experienced by the same subjects in other, short-term, frusemide experiments (Vree et al 1995b). Therefore, the urine production was measured for four days in order to find an empiric measure for the restoration of the baseline value. The recovery time was found to be 65 h, and

the total time of urine flow stimulation plus recovery time was  $6 \text{ h} + 65 \text{ h} = 71 \text{ h}$  (3 days). The reported 24-h recovery period reported by Reyes (1991) was based on a collection period of only 24 h.

During this recovery period, frusemide and its acyl glucuronide were slowly eliminated from the body with a long half-life of 20–30 h for this phase. This recovery period was named acute tolerance to frusemide diuresis in man (Hammarlund et al 1985); rebound effects were named by Reyes (1991). This recovery or rebound period coincides with the  $t_{1/2}$  of 20–30 h for both frusemide and its acyl glucuronide.

The rebound effect may be the result of a biphasic effect of frusemide or its acyl glucuronide. In concentrations or renal excretion rates  $> 20 \mu\text{g mL}^{-1}$ , there is a stimulation of the urine production, while at concentrations below this threshold there exists an inhibition of the urine production. These low renal excretion rates may exist in the slow elimination phase after administration of a therapeutic dose of 40–80 mg or higher dose, or they can be obtained after administration of 5 mg frusemide four times a day. The urine production under this low frusemide dosing regimen should be compared with baseline values of urine production in each patient or volunteer. When this was carried out in a pilot experiment, no inhibition of urine production was detected.

### Clinical implications

Cumulation of the frusemide plasma concentrations, due to the slow elimination phase, and cumulation of the rebound or recovery phase may induce a braking of the therapeutic or pharmacodynamic effect (Brater 1991).

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